ExxonMobil Chemical Company

Neoacids C5 to C28 Category Analysis Report

for the

U.S. High Production Volume Chemical Challenge Program

Prepared by:

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EXECUTIVE SUMMARY

ExxonMobil Chemical Company hereby submits the category summary report for Neoacids C5 to C28 Category under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program (Program). The purpose of this report is to:

- Present results of an assessment to determine whether six complex mixtures can be adequately characterized with existing data and additional data as described in the Neoacids C5 to C28 Category test plan.
- Summarize the SIDS (Screening Information Data Set) physicochemical, environmental fate and effects, and human health HPV Program endpoints for the Neoacids C5 to C28 Category.
- Provide a description of manufacturing processes, potential exposure sources, and uses for C5 to C28 Neoacids.

The Neoacids C5 to C28 Category is a family of trialkyl acetic acids ($R_1R_2R_3CCOOH$) that are produced by reacting a branched olefin with carbon monoxide and water at elevated temperatures and pressures in the presence of an acid catalyst. During this process, each hydrogen on the non-carboxyl carbon of acetic acid is replaced by an alkyl group. The number of carbon atoms in the category members ranges from C5 to C28.

The justification for the Neoacids C5 to C28 Category is that the members have:

- similar chemical structures,
- similar physico-chemical properties,
- comparable environmental fate,
- the same mode of action.

The data demonstrate that the category is valid for a screening-level hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-1, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6). One can assess the untested endpoints by extrapolation between and among the category members. Details are given in the subsequent chapters.

Exposure

Potential exposure to members of the Neoacids C5 to C28 Category is during company operations and is predominantly by inhalation and dermal contact. Contact can be to both vapors and aerosols of these materials. Exposure can occur during loading and unloading operations, quality control sampling, or maintenance operations. Consumer exposure is expected to be low as the materials are predominantly used as chemical intermediates and not directly sold to consumers. Limited exposure data is available. Typical exposure concentrations, where available, are well below the Occupational Exposure Limit (OEL) of 25 mg/m^3.

Human Health

Members of Neoacids C5 to C28 Category have a low order of acute toxicity by the oral, dermal, and inhalation routes of exposure. Oral LD_{50}s ranged from 1800-2000 mg/kg and dermal LD_{50}s ranged from $\geq$3160 mg/kg. Inhalation exposure studies were generally conducted at the saturated vapor pressures resulting in LC_{50}s ranging from >3.0 mg/L. The inhalation LC50 was >511 mg/m^3 when animals were exposed to neodecanoic acid aerosol.

Members of the Neoacids C5 to C28 Category are slightly to moderately irritating to the skin and the eyes. Additionally, Neoacids C5 to C28 produced moderate upper airway sensory and pulmonary irritation in male mice exposed to aerosols.

Members of the Neoacids C5 to C28 Category are not expected to be skin sensitizers in animals or humans. A member of this category did not induce sensitizing reactions in guinea pigs. Data were not available to assess the potential for respiratory tract sensitisation in animals or humans, however, since they are not expected to be skin sensitizers, it is not expected that category members would cause respiratory sensitization. Additionally, due to the low vapour pressure of members of this category, atmospheric exposure is expected to be low.

Members of the Neoacids C5 to C28 Category have a low order of subchronic toxicity by oral and dermal routes of exposure. In addition, the NOAEL for systemic toxicity following dermal exposure increases in a predictable pattern from the low to the high molecular weight end of category.

Studies carried out employing *Salmonella typhimurium* as well as *Escherichia coli* and one study with *Saccharomyces cerevisiae* JDI have not given any indications of genotoxic effects, either with or without metabolic activation. Increased chromosomal aberration was observed with fatty acids, C9-C13 neo in the presence of metabolic activation. However, other members of the category were negative in the *in vitro* chromosomal aberration assay. Additionally a negative result was seen with fatty acids, C9-C13 neo in the *in vivo* bone marrow micronucelus assay. Thus, members of the Neoacids C5 to C28 Category are not expected to be genotoxic.

Reproductive and developmental toxicity studies conducted by the oral route of exposure on members of the Neoacids C5 to C28 Category and isomers of neoacids demonstrated that these materials do not affect reproductive parameters. Although a slight increase in resorptions was observed in several of the studies, this only occurred in the highest dose group(s) and in the presence of overt maternal toxicity. These data support the conclusion that members of the Neoacids C5 to C28 Category are not selective reproductive toxicants.

In conclusion, members of the Neoacids C5 to C28 Category have a low order of acute toxicity, are not expected to skin or respiratory sensitizers, but have shown irritant effects to the skin, eyes, and upper respiratory tract. Repeated dose studies have also shown a low order of toxicity. Testing in a variety of genotoxicity assays with or without metabolic activation indicated that Neoacids C5 to C28 are not genotoxic. Reproductive/ developmental testing has shown fetal effects in some studies, but only at doses that produced overt maternal toxicity. The data support that members of the category are not selective reproductive toxicants. Thus, the toxicity of the Neoacids C5 to C28 Category has been well characterized and no further testing is proposed.

Environment

Results of the Mackay Level III environmental distribution model (Table 4) suggest a high environmental distribution into the water compartment for category members with a carbon chain length of C5 to C9. The model also predicts a high environmental distribution into the sediment compartment for neoacids in the range of C10 to C28. To illustrate the distribution trend, results of the Level III modelling, based on carbon number, are also depicted in Figure 1. However, category members are weak organic acids with estimated dissociation constants (pKa) of 4.6 to 4.9 (Karickoff, *et. al*. 1991). Consequently, category substances at neutral pH, which is typical of most natural surface waters, are expected to dissociate (>99%) to the ionized form and therefore, remain largely in water (Harris and Hayes, 1982). The Mackay model is usually limited to non-ionic organics and according to Harris and Hayes (1982), the ionized species of organic acids are generally adsorbed by soils and sediments to a much lesser degree than are the neutral forms. As a result the Mackay model may overestimate the partitioning of Neoacids C5 to C28 Category substances to the soil and sediment compartments.

Indirect photodegradation of Neoacids C5 to C28 Category substances can occur at a slow rate and, combined with their low vapor pressure, this process is not expected to contribute significantly to their degradation in the environment. Aqueous photolysis and hydrolysis are not expected to

contribute to the transformation of the neoacids in aquatic environments because they are either poorly or not susceptible to these reactions. One category member, propanoic acid, 2,2-dimethyl-, methyl ester (CAS # 598-98-1), is a carboxylic acid ester and can hydrolize to its parent neoacid, propanoic acid, 2,2-dimethyl (CAS # 75-98-9) at which point it will resist any further transformation.

Results from several standard aerobic, aquatic biodegradation tests indicate that category members will biodegrade under aerobic conditions at a slow to moderate rate (from 2.3% to 44% of biodegradation within 28 days, in ready biodegradability tests).

Based on QSAR evaluations, Neoacids C5 to C28 Category members have a low potential for bioconcentration in aquatic species (log BCF range of 0.5 to 1.0) and are not expected to bioaccumulate.

Members of the Neoacids C5 to C28 Category have been shown to exhibit low to moderate acute aquatic toxicity. This assessment is supported by the results of aquatic toxicity studies for numerous organisms. Experimental acute toxicity values for freshwater fish (96-hour LC_{50}) and invertebrates (48-hour EC_{50}) range from 630 to 37.2 mg/L and 203 to 47.1 mg/L, respectively. For algae, the experimental 72-hr EC_{50} ranges from 878 to 6.5 mg/L.

Experimental chronic aquatic toxicity data are not available for all category members. However, the potential for category members to elicit chronic aquatic toxicity has been characterized with a C7 branched and linear aliphatic acid. The 21-day EC50 value for the C7 branched and linear aliphatic acid, reported for a freshwater invertebrate, was 7.1 mg/L with a NOEC of 4.8 mg/L. As a result, the substances in this category are considered to have a low potential for chronic toxicity to aquatic organisms.

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1 IDENTITY

1.1 Identification of the Category

For purposes of the U.S. High Production Volume (HPV) Chemical Challenge Program (Program), the Neoacids C5 to C28 Category test plan submitted in December 2002 (ExxonMobil Chemical Company, 2002) included six Chemical Abstracts Service (CAS) registration numbers (RNs) (Table 1). The test plan identified existing data and additional data needed, based on an extensive technical review of the category, to adequately characterize the seven chemicals for the HPV Program endpoints.

This category analysis report summarizes HPV Program data for the Neoacids C5 to C28 Category, which contains six CAS RNs.

Table 1. CAS RNs and CAS RN Names of Members in the Neoacids C5 to C28 Category.

CAS Numbers with TSCA Names:	75-98-9	Propanoic acid, 2,2-dimethyl-
	598-98-1	Propanoic acid, 2,2-dimethyl-, methyl ester
	95823-36-2	Carboxylic acid, C6-8 neo*
	26896-20-8	Neodecanoic acid
	68938-07-8	Fatty acids C9-C13 neo
	72480-45-6	Fatty acids C9-C28 neo
CAS Numbers with Molecular Formulas:	75-98-9	C5H10O2
	598-98-1	C6H12O2
	95823-36-2	C7H14O2
	26896-20-8	C10H20O2
	68938-07-8	C12H24O2
	72480-45-6	C19H38O2

CAS Numbers with Structural Formulas:	75-98-9	CH3-C(CH3)2-COOH (based on a C5 acid; general structure; contains various methyl branching patterns)
	598-98-1	CH3-C(CH3)2-COOC (general structure; contains various methyl branching patterns)
	95823-36-2	CH3-CH2-C(CH3)(CH2-CH3)-COOH (based on a C7 acid; general structure; contains various branching patterns)
	26896-20-8	CH3-(CH2)4-C-(CH2-CH3)-CH2-COOH (based on a C10 acid; general structures; contains various branching patterns)
	68938-07-8	CH3-C(CH3)2-CH2-C(CH3)2-COOH / CH3-C(CH3)2-CH2-C((CH2)2-C(CH3)2)(CH3)-COOH (based on C9 and C13 acids; general structure; contains various branching patterns)
	72480-45-6	CH3-C(CH3)2-CH2-C(CH3)2-COOH / CH3-(CH2-C(CH3)-CH2)4-CH2-C(CH3)((CH2)6)-CH3)-COOH (based on C9 and C28 acids; general structures; contains various branching patterns)
CAS Numbers with Molecular Weights:	75-98-9	102.13
	598-98-1	116.16
	95823-36-2	130.19
	26896-20-8	172.27
	68938-07-8	200.32
	72480-45-6	298.51
CAS Numbers with Synonyms:	75-98-9	Neopentanoic acid, trimethyl acetic acid, pivalic acid
	598-98-1	Methyl pivalate
	95823-36-2	Neoheptanoic acid, 2-ethyl-2-methylbutanoic acid
	26896-20-8	Neodecanoic Acid 10
	68938-07-8	Neo 913
	72480-45-6	Neo Acid 928

* Not currently HPV but included to facilitate category evaluation.

1.2 Purity/Impurities/Additives

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Commercial 2,2-dimethyl propanoic acid (neopentanoic acid) is a clear liquid with a typical purity of 99.7%. Propanoic acid, 2,2-dimethyl, does not contain additives.

Propanoic acid, 2,2-dimethyl-, methyl ester (CAS# 598-98-1)

Commercial 2,2-dimethyl propanoic acid, methyl ester (methyl pivalate) is a clear liquid with a typical purity of 99%. Propanoic acid, 2,2-dimethyl, methyl ester does not contain additives.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Commercial carboxylic acid, C6-8 neo (neoheptanoic acid) is a clear liquid with a typical purity of 97%. The commercial product consists of C6 to C8 monocarboxylic acids with varied branching patterns. Carboxylic acid, C6-8 neo does not contain additives.

Neodecanoic acid (CAS# 26896-20-8)

Commercial neodecanoic acid is a clear liquid with a typical purity of >97%. The commercial product typically consists of branched dimethyloctanoic acid isomers. Other isomers include 2-methyl-2-ethylheptanoic and 2-methyl-2-propylhexanoic acids. Neodecanoic acid does not contain additives.

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

Commercial fatty acid, C9-C13 neo, is a clear liquid with a typical purity of 99.6%. The commercial product can be estimated at approximately 87% C9 isomers and approximately 13% C13 isomers, with the remaining isomers within the range indicated. Fatty acid, C9-C13 neo, does not contain additives.

Fatty acids, C9-C28 neo (CAS# 72480-45-6)

Commercial fatty acid, C9-C28 neo, is a clear liquid with a typical purity of 99.6%. Neoacid 928 is a complex combination of fatty acids obtained by the hydolysis of boron trifluoride esters of neoacids produced by the carboxylation and polymerization of isobutylene and nonene. It consists primarily of fatty acids having carbon numbers predominantly in the range of C9 through C28 and boiling in the range of approximately 225 to 387°C. Fatty acid, C9-C28 neo, does not contain additives.

1.3 Physico-Chemical properties

Category members have comparable structure and physical-chemical, environmental, and toxicological properties. Table 2 presents a summary of the physical-chemical properties exhibited by category members.

Table 2. Selected Physical Properties of Members in the Neoacids C5 to C28 Category.

CAS NUMBER	Chemical Name	Boiling Range [c] (º C)	Melting Point [c] (º C)	Vapor Pressure [a] (hPa @ 25ºC)	Relative Density [c] (g/cm^3)	Log [a] K_{ow}	Water Solubility [a] (mg/L @ 25ºC)
75-98-9	**Propanoic acid, 2,2-dimethyl-**	163 - 165	35 [b]	2.05	0.91	1.5 [b]	15,590
598-98-1	**Propanoic acid, 2,2-dimethyl-, methyl ester**	101	-62.5 [b]	47.6	0.87	1.8 [b]	2,835
95823-36-2	**Carboxylic acid, C6-8 neo**	207 - 210	24.6	0.325	0.93	2.4	1,912
26896-20-8	**Neodecanoic acid**	250 - 257	57.1	0.009	0.91	3.9	69
68938-07-8	**Fatty acids C9-C13 neo**	236 - 247	37 -76	0.001 - 0.061	0.92	3.3 - 5.2	3.1 - 243
72480-45-6	**Fatty acids C9-C28 neo**	236 - 247	37 - 76	<2.3E-12 - 0.061	0.92	3.3 - 6.0	<1 - 243

[a] Calculated using EPIWIN.
[b] Experimental values supplied by EPIWIN experimental database.
[c] Data supplied by ExxonMobil unpublished internal data.

1.4 Category Justification

The Neoacids C5 to C28 Category is a group of Neoacids whose physicochemical and toxicological properties are very similar and follow a regular pattern as a result of synthesis and structural similarity. The production of neoacid products involves the reaction between a branched olefin with carbon monoxide and water at elevated temperatures and pressures in the presence of an acid catalyst. The products in this category range in carbon number from C5 to C28.

The six substances share relatively similar physico-chemical properties, which suggests that their environmental fate will be similar. Neoacids are trialkylacetic acids in which each hydrogen on the non-carboxyl carbon of acetic acid has been replaced by an alkyl group. There is also a likelihood of common precursors and breakdown products that can result in structurally similar metabolites (e.g. carboxylic acid). Because these substances are similar with regard to environmental behavior/effects and human health, consideration of these substances as a category is justified.

The category also contains propanoic acid, 2,2-dimethyl-, methyl ester (CAS#: 598-98-1). This material is an ester that is rapidly hydrolyzed to the parent neoacid - propanoic acid, 2,2-dimethyl- (CAS#: 75-98-9). Because of this rapid hydrolysis, propanoic acid, 2,2-dimethyl-, methyl ester has properties for health effects, aquatic toxicity, and environmental fate that are consistent with the neoacids.

2 GENERAL INFORMATION ON EXPOSURE

Neoacids C5 to C28 Category substances are mainly used as chemical intermediates and applications of these can include the production of synthetic lubricants and hydraulic fluids,

stabilizers for PVC and alkyd resins, and drying agents in the paint and coatings industry. Exposure to substances in the Neoacids C5 to C28 Category may occur at workplaces where they are manufactured during loading and unloading operations, quality control sampling, or maintenance operations. Based on physical properties, the primary workplace exposure would be through dermal contact and inhalation and can be to both vapours and aerosols of these materials. Neoacids C5 to C28 are handled in industrial manufacturing and processing facilities and the majority of the applications involve incorporation of the acids into a matrix. Therefore, minimal consumer exposure is foreseen, since the consumer is only indirectly exposed through the use of the applications and uptake is expected to be low. Limited exposure data is available. Where available, typical exposure concentrations are well below the OEL of 25 mg/m^3.

2.1 Production Volumes and Use Pattern

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Propanoic acid, 2,2-dimethyl (neopentanoic acid) is produced by reacting isobutylene or di-isobutylene with carbon monoxide and water at elevated temperatures and pressures in the presence of an acid catalyst (Riemenschneider, 1984). Iso-butanol or *tert*-butyl alcohol may also serve as a starting material. A major use of neopentanoic acid is as a chemical intermediate in the production of synthetic lubricants or hydraulic fluids (Riemenschneider, 1984).

Propanoic acid, 2,2-dimethyl-, methyl ester (CAS# 598-98-1)

Propanoic acid, 2,2-dimethyl, methyl ester (or methyl pivalate) is made by esterifying pivalic acid or carbonylation of MTBE via the Koch process (Haubein, *et al*, 2002). A major use of Propanoic acid, 2,2-dimethyl, methyl ester is as a component in the production of vinyl chloride resins (Riemenschneider, 1984).

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Carboxylic acid, C6-8 neo is a mixture of isomeric branched carboxylic acids produced on a large scale by the Koch synthesis (Riemenschneider, 1984). The exceptional thermal stability and the resistance to oxidation and hydrolysis make it suitable as a component of synthetic lubricants or hydraulic fluids (Riemenschneider, 1984).

Neodecanoic acid (CAS# 26896-20-8)

Neodecanoic acid is produced by oxidizing the mixture of aldehydes obtained from tripropylene in the oxo process (Riemenschneider, 1984). A major use of neodecanoic acid is as a chemical intermediate in the production of drying agents, PVC stabilizers, and alkyd resins (Riemenschneider, 1984).

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

Fatty acids, C9-C13 neo is made through the hydrocarboxylation of double bond olefins in the presence of a strong acid (Brockmann, *et al*, 1984). In a second step, the intermediate product reacts with water to form a branched-chain fatty acid. Fatty acids, C9-C13 neo is frequently used in the paint and coatings industry.

Fatty acids, C9-C28 neo (CAS# 72480-45-6)

Fatty acids, C9-C28 neo is made through the hydrocarboxylation of double bond olefins in the presence of a strong acid (Brockmann, *et al*, 1984). In a second step, the intermediate product reacts with water to form a branched-chain fatty acid. Fatty acids, C9-C28 neo is frequently used in the paint and coatings industry.

2.2 Environmental Exposure and Fate

There is no information on environmental concentrations for substances in the Neoacids C5 to C28 Category.

2.2.1 Sources of Environmental Exposure

Neoacids C5 to C28 Category substances are mainly used as chemical intermediates and applications of these can include the production of synthetic lubricants and hydraulic fluids, stabilizers for PVC and alkyd resins, and drying agents in the paint and coatings industry. Essentially, Neoacids C5 to C28 released during manufacture can enter the environment through disposal of solid waste. Once in the environment they are expected to biodegrade at a slow to moderate rate. Henry's Law Constant, a measure of the potential of a molecule to evaporate from open water, indicates that the molecules comprising category substances will not volatilise at an appreciable rate. And, once in air, these molecules would not be subject to significant atmospheric degradation via hydroxyl radical attack with calculated half-lives of more than 24 hours, with the exception of Fatty Acids, C9-C28 neo, that has a half-life of approximately 6 hours. Process, storage, and handling operations are conducted in enclosed facilities. Over-spills are collected and treated (via WWTF), and air from production plants and pumping stations is collected and incinerated.

2.2.2 Photodegradation

In air, a chemical can react with photosensitized oxygen in the form of $^{\bullet}OH$ or ozone (O_3). These reactions can result in a degradative change in the parent chemical that can ultimately lead to its complete degradation. Substances in the Neoacids C5 to C28 Category do not react with $^{\bullet}OH$ in air to a significant extent, nor are they expected to react with O_3.

Potential $^{\bullet}OH$ reaction rate and atmospheric chemical half-life is calculated based on an average $^{\bullet}OH$ radical concentration. The atmospheric oxidation potential model (EPIWIN, 1999; Meylan and Howard, 1993) calculates a rate constant for the Neoacids C5 to C28 Category members ranging from 20.3E-12 to 0.7E-12 $cm^3mol^{-1}s^{-1}$ and an average atmospheric half-life ranging from 6.3 to 178.4 hours or 0.50 to 14.9 days, respectively. These values are based on a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated). The rate constants were calculated using an average global $^{\bullet}OH$ concentration of 1.5E6 $^{\bullet}OH$ /cm^3. Because the $^{\bullet}OH$ radical is produced photolytically, the $^{\bullet}OH$ radical is present at significant concentrations only during daylight hours, and its concentration exhibits a marked diurnal profile, with a maximum concentration at around solar noon (depending on cloud cover) and with low or negligible concentrations at night (Boethling and Mackay, 2000).

These data indicate that indirect photodegradation of Neoacids C5 to C28 Category substances can occur at a slow rate and, combined with their low vapour pressure, it is not expected to contribute significantly to their degradation in the environment.

Direct photochemical degradation in aqueous solution occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Substances in the Neoacids C5 to C28 Category do not absorb light within a range of 290 to 750 nm., (Boethling and Mackay, 2000) and therefore will not undergo direct photolysis. These data indicate that photolysis will not significantly contribute to the degradation of neo acids in the aquatic environment.

2.2.3 Stability in Water

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond, thereby changing the parent chemical. Chemicals that are susceptible to hydrolysis contain functional groups that can be displaced by a nucleophilic substitution reaction. Potentially hydrolyzable groups include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Harris, 1982). The lack of a suitable leaving group renders a compound resistant to hydrolysis. Carboxylic and fatty acids, such as the neo acids, are resistant to hydrolysis because they lack a functional group that is hydrolytically reactive (Harris, 1982). One category member, propanoic acid, 2,2-dimethyl-, methyl ester (CAS # 598-98-1), is a carboxylic acid ester and will rapidly hydrolize to its parent neoacid, propanoic acid, 2,2-dimethyl (CAS # 75-98-9) at which point it will resist any further transformation.

2.2.4 Transport between Environmental Compartments

Henry's Law Constants (HLCs), representing potential volatility from water, were calculated for chemicals within this category. The HLCs for the Category members range from 0.46 to 195 $Pa \cdot m^3$/mole (Table 3). These data suggest that category members would not volatilize from water and terrestrial environments at appreciable rates, with the exception of propanoic acid, 2,2-dimethyl-, methyl ester. Henry's Law constants are based on vapor pressure and water solubility values cited in Table 2, and molecular weights cited in Table 1.

Table 3. Calculated Henry's Law Constants for Members of the Neoacids C5 to C28 Category.

CAS NUMBER	Chemical Name	Henry's Law Constant (Pa-m^3/mole)
75-98-9	**Propanoic acid, 2,2-dimethyl-**	1.53
598-98-1	**Propanoic acid, 2,2-dimethyl-, methyl ester**	195
95823-36-2	**Carboxylic acid, C6-8 neo**	2.21
26896-20-8	**Neodecanoic acid**	2.37
68938-07-8	**Fatty acids C9-C13 neo**	5.05
72480-45-6	**Fatty acids C9-C28 neo**	0.46

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments (i.e., air, soil, water, sediment). Fugacity is a physical chemistry concept and can be regarded as the "escaping tendency" of a chemical from a phase (environmental compartment).

The Mackay model requires the input of basic physicochemical parameters such as molecular weight, melting point, vapor pressure, water solubility, and log K_{ow} (as found in Table 2). As stated previously, the Neoacids C5 to C28 Category members are primarily manufacturing intermediates

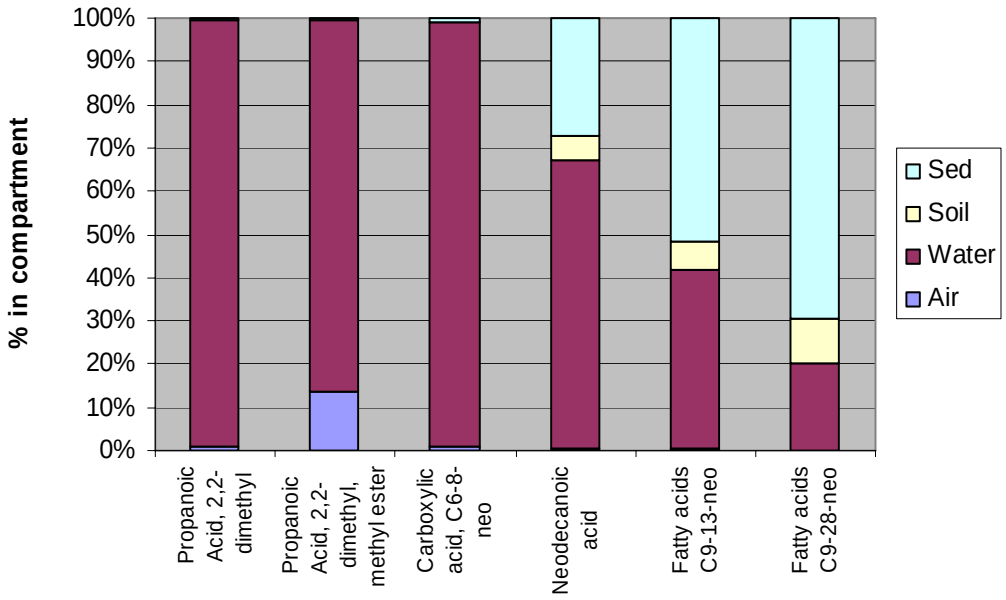
and have low volatility. As such, discharge of these products is expected to be primarily to water (*i.e.* via wastewater). Mackay Level III modeling (Mackay *et al.,* 1996; Mackay, 2003) was performed assuming 100% discharge to water. Default half-lives for degradability needed to run the model were used as per the EU Technical Guidance Document on the Use of Multimedia Models for Estimating Overall Environmental Persistence and Long-range Transport (OECD, 2004). Default half-lives were as follows: readily biodegradable (water = 5 days; soil = 30 d); pass test, but fail 10-d window (water = 10 d; soil = 90 d), fail test ≥20%, but <40% (water = 30 d; soil = 300 d), fail ready test (water = 10,000 d; soil = 30,000 d). Half-lives for sediment were 10 times that in soil. Half-lives for air were based on Atmospheric Oxidation Potential as calculated by AOPWIN version 1.89 (EPIWIN, 1999; Meylan and Howard, 1993).

Results of the Mackay Level III environmental distribution model (Table 4) suggest a high environmental distribution into the water compartment for category members with a carbon chain length of C5 to C9. The model also predicts a high environmental distribution into the sediment compartment for neoacids in the range of C10 to C28. To illustrate the distribution trend, results of the Level III modelling, based on carbon number, are also depicted in Figure 1. However, category members are weak organic acids with estimated dissociation constants (pKa) of 4.6 to 4.9 (Karickoff, *et. al*. 1991). Consequently, category substances at neutral pH, which is typical of most natural surface waters, are expected to dissociate (>99%) to the ionized form and therefore, remain largely in water (pKa of water = 15.7, Harris and Hayes, 1982). The Mackay model is usually limited to non-ionic organics and according to Harris and Hayes, 1982, the ionized species of organic acids are generally adsorbed by soils and sediments to a much lesser degree than are the neutral forms. As a result the Mackay model may overestimate the partitioning of Neoacids C5 to C28 Category substances to the soil and sediment compartments.

Table 4. Environmental Distribution as Calculated by the Mackay (2003) Level III Fugacity Model for Members of the Neoacids C5 to C28 Category.

Substance (CAS RN)	Environmental Distribution (%) per Compartment			
	Air	Water	Soil	Sediment
Propanoic acid, 2,2-dimethyl- (75-98-9)	0.78	98.7	0.27	0.26
Propanoic acid, 2,2-dimethyl-, methyl ester (598-98-1)	13.7	86.0	0.03	0.28
Carboxylic acid, C6-8 neo (95823-36-2)	0.71	98.2	0.39	0.74
Neodecanoic acid (26896-20-8)	0.28	66.7	5.7	27.3
Fatty acids C9-C13 neo (68938-07-8)	0.26	41.5	6.6	51.7
Fatty acids C9-C28 neo (72480-45-6)	0.01	20.3	10.2	69.5

Figure 1. Select Results of Fugacity Modeling Using the Mackay Level III Model for Members of the Neoacids C5 to C28 Category.



2.2.5 Biodegradation

Aerobic

Results from several standard aerobic, aquatic biodegradation tests indicate that category members will biodegrade under aerobic conditions at a slow to moderate rate (from 2.3% to 44% of biodegradation within 28 days, in ready biodegradability tests).

The manometric test procedure uses continuously stirred, closed systems, with a non-acclimated inoculum obtained from a domestic wastewater treatment plant. Percent biodegradation is based on oxygen consumption or carbon dioxide (CO_2) evolution. The continual stirring applied in these test systems is recommended when assessing the biodegradability of low to moderately water-soluble substances like those in this category.

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

In a manometric respirometry (OECD 301F) study, using non-acclimated inocula (domestic activated sludge), Propanoic acid, 2,2-dimethyl-**,** was shown to biodegrade 24% in 28 days (EMBSI, 1996a). The results of the study are based on O_2 consumption and the theoretical oxygen demand of the test chemical as calculated using results of an elemental analysis of the test chemical. This material was considered "inherently biodegradable" under the conditions of the study.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

In a manometric respirometry (OECD 301F) study, using non-acclimated inocula (domestic activated sludge), Carboxylic acid, C6-8 neo was shown to biodegrade 44% in 28 days (EMBSI, 1996a). The results of the study are based on O_2 consumption and the theoretical oxygen demand of the test chemical as calculated using results of an elemental analysis of the test chemical. This material was considered "inherently biodegradable" under the conditions of the study.

Neodecanoic acid (CAS# 26896-20-8)

In a manometric respirometry (OECD 301F) study, using non-acclimated inocula (domestic activated sludge), neodecanoic acid was shown to biodegrade 11% in 28 days (EMBSI, 1996a).

The results of the study are based on O_2 consumption and the theoretical oxygen demand of the test chemical as calculated using results of an elemental analysis of the test chemical.

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

In a manometric respirometry (OECD 301F) study, using non-acclimated inocula (domestic activated sludge), Fatty acids, C9-C13 neo was shown to biodegrade 2.3% in 28 days (EMBSI, 1996a). The results of the study are based on O_2 consumption and the theoretical oxygen demand of the test chemical as calculated using results of an elemental analysis of the test chemical.

2.2.6 Bioaccumulation

No experimental values for bioaccumulation potential are available.

Using the BCFWIN estimation program (EPIWIN, 1999), log BCF values (C5 to C28) range from 0.5 to 1.0 (BCF = 1.0 to 10), as calculated using log K_{ow} values from Table 2. Calculated BCFs for chemicals with log K_{ow} > 4 may not be reliable because the calculation methods do not account for the possibility of biotransformation.

These data suggest that category members have a low potential for bioconcentration in aquatic species and are not expected to bioaccumulate.

2.2.7 Other Information on Environmental Fate

Using the EPIWIN v.3.12 estimation program, members of the Neoacids C5 to C28 Category are expected to be removed from wastewater treatment facilities >92%. The predominant mechanism accounting for removal in a wastewater treatment facility is biodegradation, followed by partitioning of the acids to sludge, which in Europe is incinerated and in the United States is either incinerated or landfilled (personal communication EMBSI, 2005a).

2.3 Human Exposure

2.3.1 Occupational Exposure

Limited workplace exposure data are available for members of the Neoacids C5 to C28 Category (EMBSI, 1999a). Exposure to these acids can occur through dermal contact (primary route) and inhalation. Potential for worker exposure exists during manufacturing line maintenance, turnarounds, sample collection, and tank and barge loading. Limited air sampling data suggest that concentrations are well below 25 mg/m^3 (EMBSI, 1998a) for an 8-hour TWA. Personnel exposures in manufacturing facilities are low because the process, storage, and handling operations are enclosed.

There are no TLVs or other workplace guidelines for neoacids. However, ACGIH TLVs exist for low molecular weight aliphatic acids (ACGIH, 1997). The TLVs (8-hour TWA) for formic acid, acetic acid, and propionic acid are 5, 10, and 20 ppm (which are equivalent to 9, 25, and 30 mg/m^3, respectively). These concentrations were set based on human experience to prevent irritation of eyes and respiratory tract.

2.3.2 Consumer Exposure

Neoacids C5 to C28 are handled in industrial manufacturing and processing facilities and the majority of the applications involve incorporation of the acids into a matrix. Therefore, minimal consumer exposure is foreseen since the consumer is only indirectly exposed through the use of the applications and uptake is expected to be low.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Propanoic acid, 2,2-dimethyl-, methyl ester is rapidly cleaved to propanoic acid, 2,2-dimethyl-. Due to the stability conferred by the quaternary carbon, neoacids are relatively resistant to biotransformation and do not readily form bioactive metabolites. Enzymatic removal of the alkyl groups at the quaternary carbon would allow for other metabolic processes to occur. These would likely be mitochondrial beta-oxidation or by cytochrome P450 mediated omega and omega-minus-one oxidation (may be followed by beta-oxidation) to produce acetate. However, since neoacids are not readily metabolized, they would primarily be eliminated in the urine as glucoronic acid conjugates, carnitine conjugate or by dealkylation (Brass, 2002; Katz and Guest, 1994).

Studies in Animals

Test data exist on three representative neoacids: C5, C7, and C10. In pharmacokinetic studies, C5 was absorbed via oral and dermal routes of exposure. In an *in vitro* study using porcine skin, the permeability constant ($K_p \times 10^3$) of C5 was 0.2 cm/min. In comparison, the permeability constant ($K_p \times 10^3$) of other acids was 1.0 cm/min for C4 (butyric) and 0.31 cm/min for C5 (methyl butyric) (Liron and Cohen, 1984). There is no evidence of marked tissue accumulation of neoacids. Excretion pathways include urine and feces.

Limited data suggest that metabolism will vary depending on the neoacid. In rodents and monkeys, C_5 does not undergo appreciable metabolism but can form conjugated products which will facilitate excretion from the body (Brass, 2002; Vickers *et al*., 1985). The C_{10} neoacid can also form glucuronides that are rapidly eliminated from the body (Esso Research and Engineering Company, 1968b).

Studies in Humans

Data exits on neoacid C5 (pivalic acid). Human studies demonstrated the formation of pivaloylcarnitine and urinary pivaloylcarnitine excretion as the main route of C5 elimination (Brass, 2002; Vickers *et al*., 1985).

3.1.2 Acute Toxicity

Studies in Animals

Oral

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

In a toxicity study with male rats conducted on propanoic acid, 2,2-dimethyl- (CAS# 75-98-9), no deaths occurred during the 14-day observation period at levels of 34.6, 120, 417 mg/kg after

administration of a single dose by gastric intubation (Esso Research and Engineering Company, 1964). Two of the five animals at the 1450 mg/kg dose level, and all five animals at the 5000 and 10,000 mg/kg dose levels died within 48 hours. Severe depression, dyspnea, and prostration preceded death in all of the animals that died. At necropsy, congestion of lungs, liver, kidneys, and adrenals were observed in high dose animals. The acute oral LD_{50} value was 2000 mg/kg.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

An acute oral toxicity study was conducted in male rats with carboxylic acid, C6-8 neo (CAS# 95823-36-2). Animals were administered a single dose by gastric intubation at levels of 34.6, 120, 417, 1450, 5000, and 10000 mg/kg (Esso Research and Engineering Company, 1964). All five animals in the 5000 and 10000 mg/kg dose groups died within 24 hours. Prior to death, animals exhibited marked depression, sprawling of the limbs and depressed reflexes. Survivors generally appeared normal except clinical signs (depression, dyspnea and slight to marked ataxia) observed in the 1450 mg/kg dose group. Gross necropsies performed on animals from the 5000 and 10000 mg/kg dose groups revealed congested lungs, kidneys, and adrenals. No abnormalities were observed in animals from the other dose groups. From the results of the present study, it was concluded that the LD_{50} value for carboxylic acid, C6-8 neo was 1860 mg/kg.

Neodecanoic acid (CAS# 26896-20-8)

A study was conducted on neodecanoic acid (CAS# 26896-20-8) using male rats (Esso Research and Engineering Company, 1964). The animals were administered a single dose by gastric intubation at levels of 34.6, 120, 417, 1450, 5000, and 10000 mg/kg followed by a 14-day observation period. One of the five animals at the 1450 mg/kg dose level, and all five animals at the 5000 and 10,000 mg/kg dose levels died within 24 hours. All animals at the 1450 mg/kg dose level were dead by day 5 of the study. Slight to marked central nervous system (CNS) depression, dyspnea, ataxia, and/or sprawling of the limbs were observed prior to death. Necropsy findings indicated congestion of the lungs, kidneys, adrenals, liver, and/or spleen in animals at the 1450, 5000 and 10000 mg/kg dose levels. Based on the results of the present study, the oral LD_{50} value was 2000 mg/kg.

Dermal

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

An acute dermal toxicity study was conducted on propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) using male and female albino rabbits (Esso Research and Engineering Company, 1964). The animals were given a single application of the test substance at levels of 50, 200, 794, 3160 mg/kg to clipped abdominal skin under a dental dam binder. Two of four animals died at 24 and 48 hours after exposure in the highest dose group. Death was preceded by marked depression, dyspnea, prostration, excessive urination, and coma. Necropsy revealed congestion of the lungs, adrenals, kidneys, and blanched areas on the liver and spleen in animals from the 3160 mg/kg dose level. In addition, inflammation of the bladder and gastrointestinal tract were noted. The dermal LD_{50} value was 3160 mg/kg.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

The male and female albino rabbits were administered a single application of carboxylic acid, C6-8 neo (CAS# 95823-36-2) at 50, 200, 794, or 3160 mg/kg to clipped, intact abdominal skin under a dental dam binder (Esso Research and Engineering Company, 1964). One death was reported in the 200 mg/kg group at 48 hours post-exposure, but this was not considered to be treatment-related since no deaths occurred in any of the other treatment groups. Upon necropsy of the dead animal, cecal obstruction and a large amount of fluid in abdominal cavity were found. No signs of systemic toxicity were seen in any of the animals in the 50, 200, or 794 mg/kg dose groups. In the highest

dose group, marked depression, dyspnea, ataxia, and sprawling of the limbs were observed 1 – 4 hours post-exposure: however, the animals had completely recovered by 24 hours post-exposure. Necropsy revealed no significant signs of gross pathology in these animals. From the results of the present study, it was concluded that the LD_{50} value for carboxylic acid, C6-8 neo was >3160 mg/kg.

Neodecanoic acid (CAS# 26896-20-8)

A study was conducted on neodecanoic acid (CAS# 26896-20-8) using male and female rabbits (Esso Research and Engineering Company, 1964). The animals were given a single application of the test substance at 50, 200, 794, or 3160 mg/kg to clipped, intact abdominal skin under a dental dam binder. No deaths were reported with any of the doses tested. The animals appeared normal in appearance and behaviour throughout the study. The dermal LD_{50} was >3160 mg/kg.

Inhalation

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) was administered to male rats and mice for 6 hours at a saturated vapour concentration of 4.0 mg/L followed by a 14-day observation period (Esso Research and Engineering Company, 1964). All mice died within 24 hours following exposure and two rats on the second and fifth days. Hyperactivity followed by prostration was observed in mice. Rats displayed piloerection, epitasis, and dyspnea following exposure. Due to advanced autolysis, necropsy of the animals that died did not reveal any meaningful findings. Necropsy of the animals that survived until termination of the study did not reveal any significant gross pathology. The LC_{50} for mice and rats were <4.0 mg/L and >4.0 mg/L, respectively.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

No death or significant treatment-related effects were reported in rats and mice exposed to saturated carboxylic acid, C6-8 neo vapour at a concentration of 3.0 mg/L for 6 hours (Esso Research and Engineering Company, 1964). The LC_{50} for both species was >3.0 mg/L.

Neodecanoic acid (CAS# 26896-20-8)

No mortality or significant signs of toxicity were observed in rats and mice exposed to 3.0 mg/L saturated neodecanoic acid vapour for 6 hours, resulting in a LC_{50} >3.0 mg/L for both species (Esso Research and Engineering Company, 1964).

Neodecanoic acid was administered to rats, mice, and guinea pigs for 6 hours at an aerosol concentration of 511 mg/m^3 (Bio/dynamics, Inc., 1982). No mortality was reported except for one guinea pig in the control group which died on the fifth day of the post-exposure. Animals exposed to the test material exhibited some signs of laboured breathing, salivation, and eye irritation during the exposure. Upon removal from the chamber, exposed mice and guinea pigs had material-covered fur and exposed rats had some red staining around the nasal area, anogenital staining, soft stool, salivation, and lacrimation. During the 14-day post-exposure observation period, all guinea pigs appeared normal. However, some mice appeared ungroomed and some rats exhibited anogenital staining and soft stool. The LC_{50} for all three species was >511 mg/m^3.

Other Routes of Exposure

No data are available for other routes of exposure.

Studies in Humans

No data are available.

Conclusion

Members of the Neoacids C5 to C28 Category have a low order of acute toxicity by the oral, dermal, and inhalation routes of exposure. Oral LD_{50}s ranged 1860 - 2000 mg/kg and dermal LD_{50}s were ≥3160 mg/kg. Inhalation exposure studies were conducted at the saturated vapour pressures resulting in LC_{50}s ranging from >3.0 mg/L. The inhalation LC50 was >511 mg/m^3 when animals were exposed to neodecanoic acid aerosol.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

A study conducted with a single 24-hour application of propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) at levels of 50, 200, 794, 3160 mg/kg to intact rabbit skin produced irritation (Esso Research and Engineering Company, 1964). Skin irritation consisted of slight transient erythema, edema, atonia, and desquamation at the lowest level. There was a dose-dependent increase in intensity and persistence with pronounced irritation at the highest dose level characterized by blanching, eschar formation, and necrosis.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Carboxylic acid, C6-8 neo (CAS# 95823-36-2) produced dose-dependent dermal irritation to intact rabbit skin when applied for 24 hours at levels of 50, 200, 794, 3160 mg/kg (Esso Research and Engineering Company, 1964). The skin irritation ranged from slight to moderate erythema, atonia, and desquamation at the lower dose levels to moderate erythema and edema with atonia and desquamation at the two higher dose levels.

Neodecanoic acid (CAS# 26896-20-8)

A study was conducted with a single 24-hour application of neodecanoic acid (CAS# 26896-20-8) at levels of 50, 200, 794, 3160 mg/kg to intact rabbit skin (Esso Research and Engineering Company, 1964). No dermal irritation was observed at the 50 mg/kg dose level and minimal irritation characterized by slight erythema, atonia, and desquamation that subsided in 10 days was noted at the 200 mg/kg level. At the 794 and 3160 mg/kg levels, a dose-dependent increase in the degree of irritation was observed. This consisted of slight to moderate erythema, which subsided after the fourth and eighth days, and slight to moderate atonia and desquamation that diminished in severity through the 14-day observation period.

In another study, neodecanoic acid resulted in a primary irritation index of 0.67 (on a scale of 0–8) (mild irritant). A single application of 0.5 ml undiluted test substance to intact rabbit skin under semi-occlusive dressing was used on 2 male and 4 female rabbits. The mean scores at 24, 48, and 72 hours were 0.67, 0.83, and 0.67, respectively for erythema and 0.0, 0.0, and 0.0 for edema (EBSI, 1992).

Studies in Humans

No data are available.

Eye Irritation

Studies in Animals

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) was evaluated for eye irritation in rabbits (Esso Research and Engineering Company, 1964). Test material was administered in a single application to the left eye of each of six rabbits and the untreated right eye was served as a control. Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) produced eye irritation consisted of a moderate conjunctivitis in all animals at one hour, gradually diminished in severity and was last observed on the fourth day; slight iritis in two animals, persisting for 24 hours; transient dullness in one rabbit and opacity of the cornea in another rabbit with some sloughing of corneal epithelium at 24 and 48 hours. All signs of irritation disappeared after the fourth day.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Carboxylic acid, C6-8 neo (CAS# 95823-36-2) produced moderate to marked conjunctivitis which persisted for 4 to 14 days in all animals (Esso Research and Engineering Company, 1964). Slight iritis was seen in all rabbits disappearing within 48 hours. Dullness and corneal opacity with apparent sloughing and vascularisation were observed in all animals, but these reactions disappeared by the fourth and seventh days in four of the six rabbits.

Neodecanoic acid (CAS# 26896-20-8)

Neodecanoic acid (CAS# 26896-20-8) was evaluated for eye irritation in rabbits (Esso Research and Engineering Company, 1964). Moderate irritation consisting of conjunctivitis, slight transient iritis, and slight corneal opacity was observed. There was some evidence of temporary corneal damage, but the eyes of all animals were completely cleared by the seventh day of observation.

Studies in Humans

No data are available.

Respiratory Tract Irritation

Studies in Animals

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

The upper airway sensory irritation potential of carboxylic acid, C6-8 neo (CAS# 95823-36-2) was evaluated in male Swiss Webster mice using (EBSI, 1988). Four male mice per group received head-only exposures for 30 minutes to the test material generated as an aerosol at 233, 1159, 2547, and 4285 mg/m^3. Respiratory rates were monitored before, during and after exposure, to establish a baseline respiratory rate, and to evaluate the animals' sensory irritation response to the test atmosphere. There were no deaths during the exposure, or during the post-exposure period. Respiratory rates were depressed at all exposure concentrations in a dose-dependent manner which indicated sensory irritation to the upper respiratory tract. The concentration extrapolated to result in a 50% depression of respiratory rate or RD_{50} was 2912 mg/m^3. Following cessation of exposure, the degree of respiratory recovery was inversely proportional to the exposure concentration after 5-10-minute recovery period with exposure to room air.

Neodecanoic acid (CAS# 26896-20-8)

The upper airway sensory irritation potential of neodecanoic acid (CAS# 26896-20-8) was evaluated in male Swiss Webster mice using (EBSI, 1991). Four male mice per group received head-only exposures for 30 minutes to the test material generated as an aerosol at 334, 1089, and 3607 mg/m^3. Respiratory rates were monitored before, during, and after exposure to establish a baseline respiratory rate and to evaluate the animals' sensory irritation response to the test atmosphere. One of the highest concentration group mice died during the exposure. Group mean respiratory rates were depressed 24.9% and 42.5% below pre-test values in the 1089 and 3607 mg/m^3 groups, respectively, while in the 334 mg/m^3 group the rate was increased by 7.9%. The calculated value resulting in a 50% depression of respiratory rate or RD_{50} was 5491 mg/m^3.

Breathing patterns characteristic of both pulmonary and sensory irritation were observed in all treatment groups, although pulmonary irritation was the most dominant response.

Studies in Humans

No data are available.

Conclusion

Members of the Neoacids C5 to C28 Category are slightly to moderately irritating to the skin and the eyes. Additionally, Neoacids C5 to C28 produced moderate upper airway sensory and pulmonary irritation in male mice exposed to aerosols.

3.1.4 Sensitisation

Studies in Animals

Skin

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) was not a sensitizer in the Magnusson-Kligman guinea pig maximization test (Shell Research Ltd., 1977a)

Neodecanoic acid (CAS# 26896-20-8)

Neodecanoic acid (CAS# 95823-36-2) was not a sensitizer in the Magnusson-Kligman guinea pig maximization test (Shell Research Ltd., 1977b).

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

The Magnusson-Kligman maximization on fatty acids, C9-C13 neo (CAS# 68938-07-8) showed no indication of sensitization in guinea pigs (Shell Research Ltd., 1993a).

Respiratory Tract

No respiratory tract sensitisation studies have been conducted with members of the Neoacids C5 to C28 Category in animals. However, since these materials are not skin sensitizers, they would not be expected to produce respiratory tract sensitisation.

Studies in Humans

Skin

No skin sensitisation studies have been conducted with members of the Neoacids C5 to C28 Category on humans.

Respiratory Tract

No respiratory tract sensitisation studies have been conducted with members of the Neoacids C5 to C28 in humans.

Conclusion

Members of the Neoacids C5 to C28 Category are not expected to be skin sensitizers in animals or humans. A member of this category did not induce sensitizing reactions in guinea pigs. Data were not available to assess the potential for respiratory tract sensitisation in animals or humans, however, since they are not expected to be skin sensitizers, it is not expected that category members would cause respiratory sensitization. Additionally, due to the low vapour pressure of members of this category, atmospheric exposure is expected to be low.

3.1.5 Repeated Dose Toxicity Studies in Animals

Studies in Animals

Inhalation

No animal repeated dose toxicity data are available.

Oral

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Seven male and seven female rats were exposed to 0; 10; 30; 100, or 300 mg/kg/day propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) by oral gavage for 28 consecutive days (Shell Research Ltd., 1990). No treatment related changes were observed in body weight, food intake, hematology, or histopathology. The only clinical signs seen in this study were a shaking of heads, sneezing, dark nasal discharge, immediately after dosing 100 and 300 mg/kg/day. This behaviour could result from a mild irritant effect of the volatile acidic test compound. Slight increase of alkaline phosphatise, cholesterol and bilirubin levels at the 100 and 300 mg/kg/day dose levels, and slight increase of alkaline phosphatise and cholesterol levels in the plasma of females at the 30 mg/kg/day dose level. Increase in kidney and liver weight was observed in the 300 mg/kg/day group. None of these changes correlated with histopathological effects. These findings were considered adaptive changes and not indicative of a treatment-related adverse effect. The no observed adverse effect level (NOAEL) in this study was 300 mg/kg.

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

Five male and five female rats were exposed to 0; 10; 55; or 300 mg/kg/day fatty acids, C9-C13 neo (CAS# 68938-07-8) by oral gavage for 28 consecutive days (Shell Internationale Petroleum Maatschappij, 1994). There were no mortalities. Increased salivation was observed after dosing in rats receiving 300 mg/kg. No treatment related changes were observed in body weight, food consumption, hematology, or clinical chemistry. In males receiving 300 mg/kg, kidney weight increased and necropsy revealed an abnormal appearance of the kidney. A dose-related hyaline droplet was noted in males at all treatment levels. The findings in the kidney of the treated males are species and sex specific and not considered relevant to humans. The NOAEL in this study was 300 mg/kg.

Dermal

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

A repeated dose dermal toxicity study was conducted for propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) in male rabbits (Hazelton Laboratories Inc., 1964). Test material in isopropyl alcohol solution was repeatedly applied to the shaved intact skin of albino rabbits 5 days/week for two weeks (for a total of 10 applications) at doses of 30 or 300 mg/kg/day. Slight to moderate irritation at the low dose and moderate to marked irritation at the high dose was observed. Slight or moderate erythema, atonia, and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, slight to marked edema, moderate or marked atonia and desquamation. Some dermal necrosis at the site of application was seen in three rabbits and persisted throughout the study. Control animals that received only the solvent (isopropyl alcohol) showed slight irritation. There were no signs of systemic toxicity attributable to dermal absorption of propanoic acid, 2,2-dimethyl-. The NOAEL for systemic toxicity in this study was 300 mg/kg.

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Carboxylic acid, C6-8 neo (CAS# 95823-36-2) was applied at 55.4 mg/kg and 553.7 mg/kg to the shaved intact skin of rabbits for 10 applications (Hazleton Laboratories, Inc., 1964). No treatment related effects were observed on behaviour of clinical signs during the in-life phase of the study.

Gross pathology of the animals in all dose groups did not reveal any abnormalities. Repeated application of carboxylic acid C6-8 neo did produce marked skin irritation with some dermal necrosis at the site of application in the high dose group. Since no systemic effects were observed in this study, the NOAEL for systemic effects following subchronic dermal application of carboxylic acid, C6-8 neo was 553.7 mg/kg.

Neodecanoic acid (CAS# 26896-20-8)

Repeated dermal application (400 or 2800 mg/kg daily for a total of 10 applications), of undiluted Neodecanoic acid, generally produced irritation at the low dose and fissuring at the high dose (Hazleton Laboratories, Inc., 1964). Slight to moderate erythema, atonia and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, moderate to severe atonia, and desquamation with fissuring. No signs of systemic toxicity were attributed to Neodecanoic acid. Therefore, the NOAEL for systemic toxicity following subchronic dermal application of Neodecanoic acid was 2280 mg/kg.

Studies in Humans

There are no data in humans.

Conclusion

Members of the Neoacids C5 to C28 Category have a low order of toxicity under conditions of repeat exposure by oral and dermal routes. In addition, they display a consistent degree of subchronic toxicity by either oral or dermal route of exposure.

3.16 Mutagenicity

In vitro Studies

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

Mutagenic activity of propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) was evaluated in the Ames Reverse Mutation assay (Shell Research Ltd., 1978). *Salmonella typhimurium* TA 92, TA 98, TA 100, TA 1538, and *Escherichia coli* WP2 *uvr*A were overlaid on agar with or without metabolic microsomal enzyme systems (rat S9). Propanoic acid, 2,2-dimethyl- was added at concentrations of 0.01, 2, 20, 500, or 2000 µg/plate. There was no increase in reversed mutation rate either with or without metabolic activation.

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) did not increase the mitotic gene conversion frequency in *Saccharomyces cerevisiae* JDI in the presence or absence of S9 at dose levels of 0.01, 0.1, 0.1, 1.0, and 5.0 mg/ml (Shell Research Ltd., 1978).

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9) was also tested in an chromosomal aberration assay (Shell Research Ltd., 1978). RL1 rat liver cells were treated with test substance at concentrations of 0, 125, 250, and 500 µg/ml for 24 hours with and without metabolic activation. Cultures were processed for chromosome analyses and 100 cells were analyzed from each of three cultures per dose group. The top dose level resulted in 50% inhibition of cell growth in presence of S9. There was no increased incidence of chromosome aberrations in the treated cells.

Neodecanoic acid (CAS# 26896-20-8)

Mutagenic activity of neodecanoic acid (CAS# 26896-20-8) was evaluated in the bacterial reverse mutation assay (TNO, 1995a). *Salmonella typhimurium* TA 98, TA 100, TA 1535, and TA 1537 were overlaid on agar with or without metabolic microsomal enzyme systems (rat S9). Neodecanoic acid was added at concentrations of 6.17-1000 µg/plate in the absence of S9 and 18.52-1500 µg/plate in the presence of S9 mix. Concentrations up to 1500 µg/plate did not cause a

2-fold or higher increase in the number of revertant colonies of tested all *Salmonella typhimurium* strains in the presence or absence of metabolic activation.

Neodecanoic acid (CAS# 26896-20-8) was also tested for chromosomal aberration (TNO, 1995b). Two independent tests were conducted, both in the presence and absence of S9 mix. Human lymphocytes were treated with test substance at concentrations of 100-400 µg/ml in the absence of S9 and 250-800 µg/ml in the presence of S9 for 24 or 48 hours. Cultures were processed for chromosome aberrations. A mitotic index inhibition was calculated for examining cytotoxicity. There was no increased incidence of chromosome aberrations in the treated cells with or without metabolic activation. Positive control substances (mitomycin C and cyclophosphamide) confirmed the activity and sensitivity of the test system.

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

Mutagenic activity of fatty acids, C9-C13 neo (CAS# 68938-07-8) was evaluated in the bacterial reverse mutation assay (Shell Research Ltd., 1993b). *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* WP2 *uvr*A pKM 101 were overlaid on agar with or without metabolic microsomal enzyme systems (rat liver S9). Fatty acids, C9-C13 neo (CAS# 68938-07-8) was added at concentrations of 31.25-5000 µg/plate in the absence or the presence of S9. Solubility was limited at concentrations of 2000 and 5000 µg/plate. There was no increase in the number of revertants in any of the concentrations tested. The control system demonstrated system activity and sensitivity.

Fatty acids, C9-C13 neo (CAS# 68938-07-8) was also tested for chromosomal aberration (Shell Research Ltd., 1993c). Two independent tests were conducted, both in the presence and absence of S9 mix. Chinese hamster ovary (CHO-K1) cells were treated with test substance at concentrations of 13.67-250 µg/ml in the absence of S9 and 100-1000 µg/ml in the presence of S9 for 24 or 48 hours. Cultures were processed for chromosome aberrations. In the absence of rat liver S9, there was no increase in structural chromosome damage upon exposure to toxic concentrations for 48 hours. In the presence of S9 the number of cells with structural chromosomal aberrations was statistically increased at concentrations of 400 µg/ml above upon exposure for 24 and 48 hours. Positive control substances confirmed the activity and sensitivity of the test system.

In vivo Studies

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

Ten male and ten female Swiss mice were exposed to 2000 mg/kg fatty acids, C9-C13 neo (CAS # 68938-07-8) by oral gavage (TNO, 1995c). At 24 and 48 hours after dosing, femoral bone marrow was collected to evaluate micronuclei formation in polychromatic erythrocytes. No increases in the frequencies of micronuclei were observed in all groups treated with test material. Fatty acids, C9-C13 neo was negative for induction of micronuclei in this test system.

Conclusion

Adequate data are available to evaluate the genotoxicity of the Neoacids C5 to C28 category. Studies have been carried out on members of the Neoacids C5 to C28 category employing *Salmonella typhimurium* as well as *Escherichia coli* and one study with *Saccharomyces cerevisiae* JDI have not given any indications of genotoxic effects, either with or without metabolic activation. Increased chromosomal aberration was observed with fatty acids, C9-C13 neo in the presence of metabolic activation. However, other members of the category were negative in the *in vitro* chromosomal aberration assay. Additionally a negative result was seen with fatty acids, C9-C13 neo in the *in vivo* bone marrow micronucelus assay. Thus, members of the Neoacids C5 to C28 Category are not expected to be genotoxic.

3.1.6 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

Neodecanoic acid (CAS# 26896-20-8)

In a modified three-generation reproduction study, rats were exposed to 100, 500, or 1500 ppm neodecanoic acid in the diet (approximately 5, 25 and 75 mg/kg/day, respectively) through two parental and two two-litter filial generations (Hazleton Laboratories, Inc., 1968). No significant effects were observed in survival, appearance, behavior, or reproductive performance (fertility index, gestation index, live birth index, and lactation index) of the parents. No adverse effects were demonstrated in offspring on growth, appearance, or behavior. No treatment related effects were observed at gross or microscopic pathology. The NOAEL in this study was 1500 ppm. The data indicate that neodecanoic acid is not a reproductive toxicant.

Other related acids

Additional developmental toxicology data are available for isoacids, which are isomers of the neoacids. The isoacids are aliphatic carboxylic acids that have saturated branching structures. In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid (CAS#25103-52-0) at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999b). In the parental generation, there were no treatment-related effects on survival, organ weights, reproductive function, or sperm indices. In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was also conducted on isononanoic acid (CAS# 3302-10-1) (EBSI, 1998b). Rats were administered the test material in the diet at doses of 0, 600, 1200, 2500, and 5000 ppm. There were no treatment-related effects observed on mating, fertility, fecundity, or gestation indices or during sperm analysis. Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

Developmental Toxicity

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

Carboxylic acid, C6-8 neo (CAS# 95823-36-2) was examined for its effects on prenatal developmental toxicity according to OECD Guideline 414 by administering a test substance to 22 pregnant female Sprague-Dawley rats/group by oral gavage at doses of 50, 250, 600, and 800 mg/kg on gestational day 6 through day 19 (EBSI, 1986). On gestation day 20 all surviving dams were sacrificed and assessed by gross pathology (including weights of unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) were determined. From each litter the heads of half of the fetuses were preserved and examined, while the other half of the fetuses were examined for skeletal malformations and ossification variations. The high dose of 800 mg/kg produced morbidity and mortality in 4 of the 22 mated females. This group displayed lethargy, abnormal breathing, rales, and staining around the muzzle and anogenital areas. Animals in the 600 mg/kg group had a significant incidence of rales. Reduced maternal body weight gain and food consumption were observed in the 600 and 800 mg/kg dose groups. There was a decrease in mean number of live fetuses, fetal body weight, and crown-rump distance in the 800 mg/kg group.

Significant incidences of hydrocephalus, structural malformation of thoracic ribs, and incompletely ossified supraoccipital and cervical vertebrae occurred in both the 600 and 800 mg/kg groups. The NOAEL for both maternal and fetal toxicity was 250 mg/kg.

Neodecanoic acid (CAS# 26896-20-8)

In a modified three-generation reproduction study with neodecanoic acid (CAS# 26896-20-8), developmental effects were not observed in either the F1 or F2 offspring (Hazleton Laboratories, Inc., 1968). This study produced a NOAEL of 1500 ppm (in diet) for the maternal, F1, and F2 generations.

Other related acids

Additional developmental toxicology data are available for isoacids, which are isomers of the neoacids. The isoacids are aliphatic carboxylic acids that have saturated branching structures. Isooctanoic acid was tested for developmental toxicity in female rats at doses of 0, 200, 400, and 800 mg/kg/day during gestation days 6 - 15 (EBSI, 1995). At 800 mg/kg/day, maternal toxicity was observed; however, there were no effects at 400 mg/kg/day. There were no biologically significant developmental effects in this study. The no-observable-adverse-effect level (NOAEL) for maternal toxicity was 400 mg/kg/day and for developmental toxicity was 800 mg/kg/day.

In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999b). In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was conducted on isononanoic acid (EBSI, 1998b). Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

Further support for the evaluation of the potential of neoacids to be developmental toxicants comes from an analysis of the structure activity relationships that affect teratogenicity. A structure-teratogenicity analysis of carboxylic acids concluded that aliphatic acids, which have a dimethyl substitution at the C-2 position, are not developmental toxicants (Di Carlo, 1990). Furthermore, the structural requirements for carboxylic acid teratogenicity require an alpha hydrogen and a free carboxylic group. Since the neoacids are defined by their trialkyl substitution at the alpha carbon, there is no alpha hydrogen. In addition, steric hindrance of the carbonyl group by the quaternary center of the alpha carbon inhibits reactions.

Conclusion

Effects on fertility and developmental toxicity of Neoacids C5 to C28 are adequately defined with the available data on neoacids and their isomers as well as the structure-teratogenicity relationship for aliphatic acids. These data indicated that Neoacids C5 to C28 are embryo-lethal and teratogenic at maternally toxic doses but no treatment related changes in reproductive parameters were observed. These results indicate that members of the Neoacids C5 to C28 Category have a low order of reproductive and developmental toxicity.

3.2 Initial Assessment for Human Health

Members of the Neoacids C5 to C28 Category have a low order of acute toxicity by the oral, dermal, and inhalation routes of exposure. Oral LD_{50}s ranged from 1800-2000 mg/kg and dermal LD_{50}s ranged from ≥3160 mg/kg. Inhalation exposure studies were generally conducted at the saturated vapor pressures resulting in LC_{50}s ranging from >3.0 mg/L. The inhalation LC50 was >511 mg/m^3 when animals were exposed to neodecanoic acid aerosol.

Members of the Neoacids C5 to C28 Category are slightly to moderately irritating to the skin and the eyes. Additionally, Neoacids C5 to C28 produced moderate upper airway sensory and pulmonary irritation in male mice exposed to aerosols.

Members of the Neoacids C5 to C28 Category are not expected to be skin sensitizers in animals or humans. A member of this category did not induce sensitizing reactions in guinea pigs. Data were not available to assess the potential for respiratory tract sensitisation in animals or humans, however, since they are not expected to be skin sensitizers, it is not expected that category members would cause respiratory sensitization. Additionally, due to the low vapour pressure of members of this category, atmospheric exposure is expected to be low.

Members of the Neoacids C5 to C28 Category have a low order of subchronic toxicity by oral and dermal routes of exposure. In addition, the NOAEL for systemic toxicity following dermal exposure increases in a predictable pattern from the low to the high molecular weight end of category.

Studies carried out employing *Salmonella typhimurium* as well as *Escherichia coli* and one study with *Saccharomyces cerevisiae* JDI have not given any indications of genotoxic effects, either with or without metabolic activation. Increased chromosomal aberration was observed with fatty acids, C9-C13 neo in the presence of metabolic activation. However, other members of the category were negative in the *in vitro* chromosomal aberration assay. Additionally a negative result was seen with fatty acids, C9-C13 neo in the *in vivo* bone marrow micronucelus assay. Thus, members of the Neoacids C5 to C28 Category are not expected to be genotoxic.

Reproductive and developmental toxicity studies conducted by the oral route of exposure on members of the Neoacids C5 to C28 Category and isomers of neoacids demonstrated that these materials do not affect reproductive parameters. Although a slight increase in resorptions was observed in several of the studies, this only occurred in the highest dose group(s) and in the presence of overt maternal toxicity. These data support the conclusion that members of the Neoacids C5 to C28 Category are not selective reproductive toxicants.

In conclusion, members of the Neoacids C5 to C28 Category have a low order of acute toxicity, are not expected to skin or respiratory sensitizers, but have shown irritant effects to the skin, eyes, and upper respiratory tract. Repeated dose studies have also shown a low order of toxicity. Testing in a variety of genotoxicity assays with or without metabolic activation indicated that Neoacids C5 to C28 are not genotoxic. Reproductive/ developmental testing has shown fetal effects in some studies, but only at doses that produced overt maternal toxicity. The data support that members of the category are not selective reproductive toxicants. Thus, the toxicity of the Neoacids C5 to C28 Category has been well characterized and no further testing is proposed.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Propanoic acid, 2,2-dimethyl- (CAS# 75-98-9)

The acute toxicity of propanoic acid, 2,2-dimethyl- (neopentanoic acid) was investigated with a freshwater fish (*Crassius auratus*) following Method 231 of Standard Methods for the Examination of Water and Wastewater (APHA, 1971). Test solutions were prepared by directly adding neopentanoic acid to 25 liters of laboratory water, in glass aquaria, at a temperature of approximately 20°C. A series of concentrations was tested and conducted under static conditions. The duration of the test was 96 hours and the solutions were aerated throughout the test. The 96-hour LC_{50} was 380 mg/L as determined by linear interpolation and is based on measured concentrations (Bridie, et al, 1979).

Propanoic acid, 2,2-dimethyl- (neopentanoic acid) was also investigated for its effects on the freshwater invertebrate (*Daphnia magna*) following U.S. EPA 660/3-75-009 Environmental Effects test guidelines. The study was conducted under static conditions. Individual treatments were prepared by adding varying amounts of the test substance, in ethanol, directly to 500 ml of dilution water in glass beakers. After mixing, the solutions were divided into three 150 ml replicates at each concentration level with 5 daphnids in each replicate. Nominal levels were 0, 36, 60, 100, 170, 280 and 460 mg/L. A positive control (with ethanol) was also tested. The 48-hour EL_{50} was 203 mg/L based on nominal loading levels (EG&G, 1977a).

An acute experimental value is also reported for a freshwater green alga (*Pseudokirchneriella subcapitata*). Propanoic acid, 2,2-dimethyl- was tested following OECD 201 test guidelines. Individual WAFs were prepared at nominal levels of 0, 62, 125, 250, 500, and 1000 mg/L in algal nutrient media. Each test replicate was inoculated with 1.0×10^4 algal cells/mL and placed on an oscillating table under continuous lighting. Under static conditions, the 72-hour EC_{50} values based on biomass and growth rate were 878 and >979 mg/L, respectively, with corresponding No Observed Effect Concentrations (NOEC) values of 246 mg/L (EMBSI, 2003a).

Carboxylic acid, C6-8 neo (CAS# 95823-36-2)

The acute toxicity of Carboxylic acid, C6-8 neo was investigated with a freshwater fish (*Pimephales promelas*) using a C7 acid (approximately 70% n-heptanoic acid, 30% iso-heptanoic acid) following test procedures developed by the U.S. EPA (EPA TSCA 797.1400). The study was conducted under flow-through conditions. A stock solution was prepared daily at a nominal concentration of 900 mg/L. The stock solution was delivered to the test chambers via a diluter system where it prepared test treatments at nominal levels of 0, 56.25, 112.5, 225, 450, and 900 mg/L. Measured concentrations were <0.8, 51.4, 125, 200, 436, and 882 mg/L. Twenty fish were tested at each concentration level. The 96-hour LC_{50} was 630 mg/L based on measured values (EMBSI, 1993a).

Carboxylic acid, C6-8 neo was also investigated for its effects on the freshwater invertebrate (*Daphnia magna*) using a C7 acid (approximately 70% n-heptanoic acid, 30% iso-heptanoic acid) following test procedures developed by the U.S. EPA (EPA TSCA 797.1300). The study was conducted under flow-through conditions. A stock solution was prepared daily at a nominal concentration of 900 mg/L. The stock solution was delivered to the test chambers via a diluter system where it prepared test treatments at nominal levels of 0, 56.25, 112.5, 225, 450, and 900 mg/L. Measured concentrations were <0.8, 54.7, 107, 222, 476, and 903 mg/L. Twenty daphnids

were tested at each concentration level. The 48-hour EC_{50} was 138 mg/L based on measured values (EMBSI, 1993b).

An acute experimental value was also reported for the freshwater alga (*Pseudokirchneriella subcapitata*). Data was developed for carboxylic acid, C6-8 neo using a C7 acid (approximately 70% n-heptanoic acid, 30% iso-heptanoic acid) following test procedures developed by the U.S. EPA (EPA TSCA 797.1050). The study was conducted under static conditions. A stock solution was prepared at a nominal concentration of 500 mg/L. The 500 mg/L stock solution was diluted with algal nutrient media to prepare test treatments at nominal levels of 0, 3.12, 6.25, 12.5, 25, and 50 mg/L. Measured concentrations were <0.8, 3.03, 6.20, 12.24, 23.55, and 52.15 mg/L. The 96-hour EC_{50} value based on growth rate was 6.5 mg/L based on measured values, with corresponding EC_{10} and EC_{90} values of 3.7 and 53.5 mg/L, respectively (EMBSI, 1993c). The corresponding No Observed Effect Concentration (NOEC) value was 3.0 mg/L.

Neodecanoic acid (CAS# 26896-20-8)

The acute toxicity of neodecanoic acid was investigated with a freshwater fish (*Oncorhynchus mykiss*) following OECD 203 test guidelines. The study was conducted using static-renewal procedures with approximately 80% of the test solution in each test replicate renewed at 24-hour intervals. Test treatments were prepared as Water Accommodated Fractions (WAFs) at nominal levels of 0, 6.25, 12.5, 25, 50, and 100 mg/L. Measured concentrations were 0, 10.3, 13.6, 26.3, 52.5, and 102 mg/L. The pH of the test solutions ranged from 7.0 to 7.6 during the study. Fifteen fish were tested at each concentration level. The 96-hour LC_{50} was 37.2 mg/L based on measured values (EMBSI, 1996b).

Neodecanoic acid was also investigated for its effects on the freshwater invertebrate (*Daphnia magna*) following U.S. EPA 660/3-75-009 Environmental Effects test guidelines. The study was conducted under static conditions. Individual treatments were prepared by adding varying amounts of the test substance dissolved in triethylene glycol (TEG) to 500 ml of dilution water in glass beakers. Three replicates of 150 ml each were prepared at each treatment level. Nominal levels were 0, 13, 22, 36, 60, 100, 170 and 280 mg/L. A positive TEG control and a negative (dilution water) control were also tested. The pH of the test solutions ranged from 7.1 to 8.2 during the study. The 48-hour EL_{50} was 47.1 mg/L based on nominal loading levels (EG&G, 1977b).

Fatty acids, C9-C13 neo (CAS# 68938-07-8)

The acute toxicity of fatty acids, C9-C13 neo was investigated with a freshwater fish (*Oncorhynchus mykiss*) following OECD 203 test guidelines. The study was conducted using static-renewal procedures with approximately 80% of the test solution in each test replicate renewed at 24-hour intervals. Test treatments were prepared as Water Accommodated Fractions (WAFs) at levels of 0, 6.31, 12.4, 25, 59, and 104 mg/L, based on the actual loading of the test substance. Measured concentrations were 0, 5.18, 10.5, 23, 61, and 101 mg/L. The pH of the test solutions ranged from 6.3 to 8.0 during the study. Ten fish were tested at each concentration level. The 96-hour LC_{50} was 37.5 mg/L based on measured values (EMBSI, 2003b).

The acute toxicity of fatty acids, C9-C13 neo was also investigated for its effects on the freshwater invertebrate (*Daphnia magna*) following OECD 202 test guidelines. Individual WAFs were prepared at nominal levels of 0, 6, 13.5, 26, 52, and 102 mg/L, based on the actual loading of the test substance. Measured concentrations were 0, 6.22, 11.5, 23.5, 45.6, and 84.9 mg/L. The pH of the test solutions ranged from 6.7 to 8.2 during the study. Twenty daphnids were tested at each concentration level. The 48-hour EC_{50} was 62.2 mg/L based on measured values (EMBSI, 2003c).

An acute experimental value is also reported for a freshwater green alga (*Pseudokirchneriella subcapitata*). Fatty acids, C9-C13 neo was tested following OECD 201 test guidelines. Individual WAFs were prepared at nominal levels of 0, 64.5, 125, 247, 531, and 1054 mg/L in algal nutrient media, based on the actual loading of the test substance. Measured concentrations were 0, 62.4,

120, 226, 350, and 432 mg/L. Each test replicate was inoculated with 1.0 x 10^4 algal cells/mL and placed on an oscillating table under continuous lighting. Under static conditions, the 72-hour EC_{50} values based on biomass and growth rate were 216 and 388 mg/L, respectively, with corresponding No Observed Effect Concentrations (NOEC) values of 226 mg/L (EMBSI, 2003d).

Table 5. Acute Aquatic Toxicity of Members of the Neoacids C5 to C28 Category.

Substance (CAS #)	Propanoic Acid, 2,2-dimethyl- (75-98-9)	Propanoic Acid, 2,2-dimethyl-, methyl ester (598-98-1)	Carboxylic Acid, C6-C8 neo (95823-36-2)	Neodecanoic Acid (26896-20-8)	Fatty Acids, C9-C13 neo (68938-07-8)	Fatty Acids, C9-C28 neo (72480-45-6)
Fish Acute Toxicity (96-hour)	LC_{50} = 380 mg/L (Bridie, 1979)	ra	LC_{50} = 630 mg/L* (EMBSI, 1993a)	LC_{50} = 37.2 mg/L (EMBSI, 1993a)	LC_{50} = 37.5 mg/L (EMBSI, 2003b)	ra
***Daphnid* Acute Toxicity (48-hour)**	EL_{50} = 203 mg/L (EG&G, 1977a)	ra	EC_{50} = 138 mg/L* (EMBSI, 1993b)	EL_{50} = 47.1 mg/L (EG&G, 1977b)	EC_{50} = 62.2 mg/L (EMBSI, 2003c)	ra
Alga Toxicity (72-hour)	EC_{50} = 878 mg/L (EMBSI, 2003a)	ra	EC_{50} = 6.5 mg/L* (EMBSI, 1993c)	ra	EC_{50} = 216 mg/L (EMBSI, 2003d)	ra

ra Read-across

* Data are for a C7 branched and linear aliphatic acid product that does not contain a quaternary carbon, but is used to read across to a C6-8 neoacid product. The alga study results are for a 96-hour study.

Chronic Toxicity Test Results

Experimental chronic toxicity data exists for a single C7 analog material. Carboxylic acid, C6-8 neo was investigated for its chronic effects on the freshwater invertebrate (*Daphnia magna*) using a C7 acid (approximately 70% n-heptanoic acid, 30% iso-heptanoic acid) following test procedures developed by the U.S. EPA (EPA TSCA 797.1330). The study was conducted under flow-through conditions for a period of 21 days. A stock solution was prepared daily at a nominal concentration of 50 mg/L. The stock solution was delivered to the test chambers via a diluter system where it prepared test treatments at nominal levels of 0, 3.12, 6.25, 12.5, 25, and 50 mg/L. Measured concentrations were <0.9, 2.32, 4.78, 10.1, 21.7, and 44.4 mg/L. The flow of the solution through the test was equal to at least 6 times the volume of the test chambers in a 24-hour period. Forty daphnids were tested at each concentration level. The 21-day EC_{50} was 7.1 mg/L based on measured values (EMBSI, 1994a). The No Observed Effect Concentration (NOEC) and Lowest Observed Effect Concentration (LOEC) for Adult Immobilization was 4.78 and 10.1 mg/L, respectively. The NOEC and LOEC values for Offspring per Adult were 4.78 and 10.1 mg/L, respectively. The Maximum Acceptable Toxicant Concentration (MATC), which is the maximum concentration at which the test chemical can be present and not be toxic to the organism, was 6.93 mg/L, and was based on adult immobilization and number of young per adult.

Reliable QSAR measurements are not available for acids (Cash and Nabholz, 1990). However, the substances in this category have a low potential for chronic exposure of aquatic organisms as physical loss processes are expected to contribute to their overall degradation.

4.2 Initial Assessment for the Environment

Results of the Mackay Level III environmental distribution model (Table 4) suggest a high environmental distribution into the water compartment for category members with a carbon chain length of C5 to C9. The model also predicts a high environmental distribution into the sediment

compartment for neoacids in the range of C10 to C28. To illustrate the distribution trend, results of the Level III modelling, based on carbon number, are also depicted in Figure 1. However, category members are weak organic acids with estimated dissociation constants (pKa) of 4.6 to 4.9 (Karickoff, *et. al*. 1991). Consequently, category substances at neutral pH, which is typical of most natural surface waters, are expected to dissociate (>99%) to the ionized form and therefore, remain largely in water (Harris and Hayes, 1982). The Mackay model is usually limited to non-ionic organics and according to Harris and Hayes (1982), the ionized species of organic acids are generally adsorbed by soils and sediments to a much lesser degree than are the neutral forms. As a result the Mackay model may overestimate the partitioning of Neoacids C5 to C28 Category substances to the soil and sediment compartments.

Indirect photodegradation of Neoacids C5 to C28 Category substances can occur at a slow rate and, combined with their low vapor pressure, this process is not expected to contribute significantly to their degradation in the environment. Aqueous photolysis and hydrolysis are not expected to contribute to the transformation of the neoacids in aquatic environments because they are either poorly or not susceptible to these reactions. One category member, propanoic acid, 2,2-dimethyl-, methyl ester (CAS # 598-98-1), is a carboxylic acid ester and can hydrolize to its parent neoacid, propanoic acid, 2,2-dimethyl (CAS # 75-98-9) at which point it will resist any further transformation.

Results from several standard aerobic, aquatic biodegradation tests indicate that category members will biodegrade under aerobic conditions at a slow to moderate rate (from 2.3% to 44% of biodegradation within 28 days, in ready biodegradability tests).

Based on QSAR evaluations, Neoacids C5 to C28 Category members have a low potential for bioconcentration in aquatic species (log BCF range of 0.5 to 1.0) and are not expected to bioaccumulate.

Members of the Neoacids C5 to C28 Category have been shown to exhibit low to moderate acute aquatic toxicity. This assessment is supported by the results of aquatic toxicity studies for numerous organisms. Experimental acute toxicity values for freshwater fish (96-hour LC_{50}) and invertebrates (48-hour EC_{50}) range from 630 to 37.2 mg/L and 203 to 47.1 mg/L, respectively. For algae, the experimental 72-hr EC_{50} ranges from 878 to 6.5 mg/L.

Experimental chronic aquatic toxicity data are not available for all category members. However, the potential for category members to elicit chronic aquatic toxicity has been characterized with a C7 branched and linear aliphatic acid (Table 6). The 21-day EC50 value for the C7 branched and linear aliphatic acid, reported for a freshwater invertebrate, was 7.1 mg/L with a NOEC of 4.8 mg/L. As a result, the substances in this category are considered to have a low potential for chronic toxicity to aquatic organisms.

5 DATA SUMMARY

Physico-chemical, environmental fate and effects, and human health data that characterize the six products in the Neoacids C5 to C28 Category are summarized in Tables 6 and 7.

Table 6. Summarized Physico-Chemical and Environmental Data for Members of the Neoacids C5 to C28 Category.

Endpoint	Neoacids C5 to C28 Category Members and CAS RNs					
	Propanoic Acid, 2,2-dimethyl-	**Propanoic Acid, 2,2-dimethyl-, methyl ester**	**Carboxylic Acid, C6-C8 neo**	**Neodecanoic Acid**	**Fatty Acids, C9-C13 neo**	**Fatty Acids, C9-C28 neo**
	75-98-9	**598-98-1**	**95823-36-2**	**26896-20-8**	**68938-07-8**	**72480-45-6**
Melting Point or Range (a) (°C)	35	-62.5	24.6	57.1	37 to 76	37 to 76
Boiling Point or Range (a) (°C)	163 to 165	101	207 to 210	250 to 257	236 to 246	236 to 246
Vapor Pressure (a) (hPa)	2.05	47.6	0.325	0.009	0.001 to 0.061	<2.3E-12 to 0.061
Log K_{ow} (a)	1.5	1.8	2.4	3.9	3.3 to 5.2	3.3 to 6.0
Water Solubility (a) (mg/L)	15,590	2,835	1,912	69	3.1 to 243	<1 to 243
Direct Photodegradation	Direct photolysis will not contribute to degradation					
Indirect (OH-) Photodegradation (half-life, hrs) (b)	126	178	38.9	17.0	12.4	12.4
Hydrolysis	Hydrolysis will not contribute to degradation					
Distribution	Predominantly in water				Predominantly in sediment and water	

a Ranges are based on constituent data.
b Atmospheric half-life values are based on a 12-hr day.

Table 6. Continued.

Endpoint	Neoacids C5 to C28 Category Members and CAS RNs					
	Propanoic Acid, 2,2-dimethyl-	**Propanoic Acid, 2,2-dimethyl-, methyl ester**	**Carboxylic Acid, C6-C8 neo**	**Neodecanoic Acid**	**Fatty Acids, C9-C13 neo**	**Fatty Acids, C9-C28 neo**
	75-98-9	**598-98-1**	**95823-36-2**	**26896-20-8**	**68938-07-8**	**72480-45-6**
Biodegradation (% after 28 days)	24	24 to 44 (ra)	44	11	2.3	2.3 (ra)
96-hr Fish LC_{50} (mg/L)	380	380 (ra)	630 (ra: C7 linear and branched acid)	37.2	37.5	37.5 (ra)
48-hr Invertebrate EC_{50} (mg/L)	203	203 (ra)	138 (ra: C7 linear and branched acid)	47.1	62.2	62.2 (ra)
72-hr Alga EC_{50} (mg/L)	878 b >979 gr	878 b >979 gr (ra)	6.5 b* (ra: C7 linear and branched acid)	216 b 388 gr (ra)	216 b 388 gr	216 b 388 gr (ra)
72-hr Alga NOEC (mg/L)	246 b 246 gr	246 b 246 gr (ra)	3.0 b* (ra: C7 linear and branched acid)	226 b 226 gr (ra)	226 b 226 gr	226 b 226 gr (ra)
21-day Invertebrate EC_{50} (mg/L)	7.1 (ra: C7 linear and branched acid)	7.1 (ra: C7 linear and branched acid)	7.1	<7.1 (ra: C7 linear and branched acid)	<7.1 (ra: C7 linear and branched acid)	<7.1 (ra: C7 linear and branched acid)
21-day Invertebrate NOEC (mg/L)	4.8 (ra: C7 linear and branched acid)	4.8 (ra: C7 linear and branched acid)	4.8	<4.8 (ra: C7 linear and branched acid)	<4.8 (ra: C7 linear and branched acid)	<4.8 (ra: C7 linear and branched acid)

b biomass
gr growth rate
ra Based on read-across data from other members of the category or analog substances from outside the category (analog substances are identified).
* 96-hr EC_{50}

Table 7. Summarized Human Health Data for Members of the Neoacids C5 to C28 Category.

Endpoint	Neoacids C5 to C28 Category Members and CAS RNs					
	Propanoic Acid, 2,2-dimethyl-	**Propanoic Acid, 2,2-dimethyl-, methyl ester**	**Carboxylic Acid, C6-C8 neo**	**Neodecanoic Acid**	**Fatty Acids, C9-C13 neo**	**Fatty Acids, C9-C28 neo**
	75-98-9	**598-98-1**	**95823-36-2**	**26896-20-8**	**68938-07-8**	**72480-45-6**
Acute Oral LD_{50} (rat) (mg/kg)	2000	1860 (ra)	1860	2000	2000 (ra)	2000 (ra)
Acute Dermal LD_{50} (rabbit) (mg/kg)	3160	3160 (ra)	>3160	>3160	>3160 (ra)	>3160 (ra)
Acute 6-hr Inhalation LC_{50}	<4.0 mg/L (mouse) >4.0 mg/L (rat)	>3.0 mg/L (mouse, rat) (ra)	>3.0 mg/L (mouse, rat)	>3.0 mg/L (mouse, rat) >511 mg/m^3 (aerosol) (mouse, rat, guinea pig)	>3.0 mg/L (mouse, rat) >511 mg/m^3 (aerosol) (mouse, rat, guinea pig) (ra)	>3.0 mg/L (mouse, rat) >511 mg/m^3 (aerosol) (mouse, rat, guinea pig) (ra)
Irritation	Moderate irritant (eyes) Moderate irritant (skin) Moderate irritant (respiratory tract) (ra)	Moderate irritant (eyes) (ra) Moderate irritant (skin) (ra) Moderate irritant (respiratory tract) (ra)	Moderate irritant (eyes) Moderate irritant (skin) Moderate irritant (respiratory tract)	Moderate irritant (eyes) Slight irritant (skin) Moderate irritant (respiratory tract)	Moderate irritant (eyes) (ra) Slight irritant (skin) (ra) Moderate irritant (respiratory tract) (ra)	Moderate irritant (eyes) (ra) Slight irritant (skin) (ra) Moderate irritant (respiratory tract) (ra)

Table 7. Continued.

Endpoint	Neoacids C5 to C28 Category Members and CAS RNs					
	Propanoic Acid, 2,2-dimethyl-	**Propanoic Acid, 2,2-dimethyl-, methyl ester**	**Carboxylic Acid, C6-C8 neo**	**Neodecanoic Acid**	**Fatty Acids, C9-C13 neo**	**Fatty Acids, C9-C28 neo**
	75-98-9	**598-98-1**	**95823-36-2**	**26896-20-8**	**68938-07-8**	**72480-45-6**
Mutagenicity Ames Assay	Negative	Negative (ra)	Negative (ra)	Negative	Negative	Negative (ra)
Mutagenicity Mouse Micronucleus	Negative (ra)	Negative (ra)	Negative (ra)	Negative (ra)	Negative	Negative (ra)
Repeat Dose Toxicity NOAEL (rat) (mg/kg/day)	300 (oral) 300 (dermal)	300 (oral) 300 (dermal) (ra)	553.7 (dermal)	2280 (dermal)	300 (oral)	300 (oral) (ra)
Reproductive Toxicity NOAEL (rat) (ppm)	7500 (ra: isooctanoic acid)	7500 (ra: isooctanoic acid)	7500 (ra: isooctanoic acid)	1500	1200 (ra: isononanoic acid)	1200 (ra: isononanoic acid)
Developmental Toxicity NOAEL (rat) (mg/kg/day)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)	250 (m) 250 (f) 400 (m) 800 (f) (ra: isooctanoic acid)

ra Based on read-across data from other members of the category or analog substances from outside the category (analog substances are identified).
m maternal
f fetal

6 REFERENCES

- ACGIH (1997). American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents, Cincinnati, OH, USA.
- APHA (1971). Standard Methods for the Examination of Water and Wastewater, American Public Health Association, Inc., New York. Method No, 231.
- Bio/dynamics, Inc. (1982). Evaluation of the Acute Inhalation Toxicity of Neodecanoic Acid in Rats, Mice, and Guinea Pigs. Unpublished report.
- Boethling R and Mackay D (2000). Handbook of Property Estimation Methods for Chemicals. CRC Press, Boca Raton, FL, USA.
- Brass E (2002). Pivalate-generating Prodrugs and Carnitine Homeostasis in Man. Pharmacol. Rev. 54(4): 589-598.
- Bridie A, Wolff C and Winter M (1979). The Acute Toxicity of Some Petrochemicals to Goldfish. Water Research. Vol. 13.
- Brockman R, Demmering G, Kreutzer U, Lindemann M, Plachenka J and Steinberner U (1984). In: *Ullman's Encyclopedia of Industrial Chemistry*, 5th completely revised ed., Vol. A10, VCH Publishers, pp. 245-275.
- Cash G and Nabholz V (1990). ECOSAR. U.S. Environmental Protection Agency, Office of Pesticide, Pollution, and Toxics - Risk Assessment Division. Washington, DC, USA.
- DiCarlo F (1990). Structure-Activity Relationships (SAR) and Sturcture-Metabolism Relationships (SMR) Affecting the Teratogenicity of Carboxylic Acids. Drug Metabolism Reviews. 22(5): 441-449.
- EG&G (1977a). EG&G Bionomics, Wareham, MA, USA. Acute Toxicity of C5 Neo acid to Water Flea, *Daphnia magna*. Project # BW-78-1-004.
- EG&G (1977b). EG&G Bionomics, Wareham, MA, USA. Acute Toxicity of C10 Neo acid to Water Flea, *Daphnia magna*. Project # BW-78-1-005.
- EPIWIN (1999). Estimation Program Interface for Windows, version 3.04. Syracuse Research Corporation, Syracuse, NY, USA.
- Esso Research and Engineering Company (1964). Acute Oral, Dermal, Eye Irritation and Inhalation Toxicity. Unpublished report.
- Esso Research and Engineering Company (1968a). Radiotracer Metabolism Study Neodecanoic Acid-1-^{14}C. Unpublished report.
- EBSI (1986). Exxon Biomedical Sciences, Inc. Oral Teratology Study in Rats. Unpublished report.
- EBSI (1988). Exxon Biomedical Sciences, Inc. Evaluation of the Respiratory Sensory Irritation Potential in Mice of Neo Heptanoic Acid. Unpublished report.
- EBSI (1991). Exxon Biomedical Sciences, Inc. Upper Airway Sensory Irritation Study in the Mouse. Unpublished report.
- EBSI (1992). Exxon Biomedical Sciences, Inc. Primary Dermal Irritation Study in the Rabbit. Unpublished report.
- EMBSI (1993a). ExxonMobil Biomedical Sciences, Inc. Fish Acute Flow-Through Toxicity Test. Study No. 148641. Unpublished report.

- EMBSI (1993b). ExxonMobil Biomedical Sciences, Inc. *Daphnia* Acute Flow-Through Toxicity Test. Study No. 148664. Unpublished report.
- EMBSI (1993c). ExxonMobil Biomedical Sciences, Inc. Algal Acute Toxicity Test. Study No. 148667. Unpublished report.
- EMBSI (1994a). ExxonMobil Biomedical Sciences, Inc. Daphnia sp., Chronic Flow-through Toxicity Test. Study No. 178545. Unpublished report.
- EMBSI (1996a). ExxonMobil Biomedical Sciences, Inc. Ready Biodegradation: OECD 301F Manometric Respirometry Test. Study No. 136894a. Unpublished report.
- EMBSI (1996b). ExxonMobil Biomedical Sciences, Inc. Fish Acute Toxicity Test. Study No. 118358. Unpublished report.
- EMBSI (1998a). ExxonMobil Biomedical Sciences, Inc. Product Stewardship Risk Assessment: Neo Acids.
- EMBSI (1998b). ExxonMobil Biomedical Sciences, Inc. One Generation Reproduction Toxicity Range-Finding Study in Rats. Unpublished report.
- EMBSI (1999a). ExxonMobil Biomedical Sciences, Inc. ExxonMobil Occupational Exposure Limit: C5 to C13 Neoacids. Unpublished report.
- EMBSI (1999b). ExxonMobil Biomedical Sciences, Inc. One Generation Reproduction Toxicity Range-Finding Study in Rats. Unpublished report.
- EMBSI (2003a). ExxonMobil Biomedical Sciences, Inc. Alga, Growth Inhibition Test. Study No. 145467. Unpublished report.
- EMBSI (2003b). ExxonMobil Biomedical Sciences, Inc. Fish, Acute Toxicity Test. Study No. 145658. Unpublished report.
- EMBSI (2003c). ExxonMobil Biomedical Sciences, Inc. Daphnia sp., Acute Immobilization Test. Study No. 145642A. Unpublished report.
- EMBSI (2003d). ExxonMobil Biomedical Sciences, Inc. Alga, Growth Inhibition Test. Study No. 145667. Unpublished report.
- EMBSI. (2005a). ExxonMobil Biomedical Sciences, Inc. personal communication.
- ExxonMobil Chemical Company (2003a). Neo Pentanoic Acid. Unpublished report.
- ExxonMobil Chemical Company (2003b). Methyl Pivalate. Unpublished report.
- ExxonMobil Chemical Company (2003c). Neo Heptanoic Acid. Unpublished report.
- ExxonMobil Chemical Company (2003d). Neo Decanoic Acid. Unpublished report.
- ExxonMobil Chemical Company (2003e). Neo Acid 913. Unpublished report.
- ExxonMobil Chemical Company (2003f). Neo Acid 928. Unpublished report.
- Harris J (1982). Rate of Hydrolysis. In: Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. 7, 1-48. Lyman W, Reehl W and Rosenblatt D (eds.). McGraw Hill, New York, NY, USA.
- Harris J and Hayes M (1982). Acid Dissociation Constant. In: Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. 6, 1-28. Lyman W, Reehl W and Rosenblatt D (eds). McGraw Hill, New York, NY, USA.

- Haubein N, Broadbelt L, Mozeleski E, Schlosberg R, Cook R, Mehnert C, Farcasiu D (2002). 13C NMR Study of the Acid-Catalyzed Carbonylation of Methyl *tert*-Butyl Ether (MTBE). Catalysis Letters 80 (3-4): 139-145.
- Hazelton Laboratories, Inc. (1964). Repeated Dermal Application – Rabbits. Unpublished report.
- Hazelton Laboratories, Inc. (1968). Modified Three-generation Reproduction Study – Rats. Unpublished report.
- Karickoff S, McDaniel V, Melton C, Vellino A, Nute D, Carreira L (1991). Predicting chemical reactivity by computer. Environ. Toxicol. Chem. 10: 1405-1416.
- Katz G and Guest D (1994). Aliphatic Carboxylic Acids. In: Patty's Industrial Hygiene and Toxicology, Fourth Edition, Volume 2, Part E. Clayton G and Clayton F (eds). Published by John Wiley & Sons, Inc. New York, NY, USA.
- Liron Z and Cohen S (1984). Percutaneous Absorption of Alkanoic Acids II: Application of Regular Solution Theory. Journal of Pharmaceutical Sciences 73 (4): 538-542.
- Mackay D, Di Guardo A, Paterson S and Cowan C (1996). Evaluating the environmental fate of a variety of types of chemicals using the EQC model. Environ. Toxicol. Chem. 15: 1627-1637.
- Mackay D (1998). Level I Fugacity-Based Environmental Equilibrium Partitioning Model, Version 2.1 (16-bit). Environmental Modelling Centre, Trent University, Ontario, Canada.
- Meylan W and Howard P (1993). Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26: 2293-2299.
- Riemenschneider W (1984). In: *Ullman's Encyclopedia of Industrial Chemistry*, 5th completely revised ed., Vol. A5, VCH Publishers, 1984, pp. 235-248.
- Shell Internationale Petroleum Maatschappij (1994). Versatic 913D: 28-Day Oral (Gavage Administration) Sub-chronic Toxicity Study in the Rat. Unpublished report.
- Shell Research Ltd. (1977a). Toxicology of Fine Chemicals: Acute Toxicity, Skin and Eye Irritancy and Skin Sensitizing Potential of Pivalic Acid. Unpublished report.
- Shell Research Ltd. (1977b). TLGR 0024.77. Unpublished report.
- Shell Research Ltd. (1978). Toxicity Studies with Pivalic Acid: *In Vitro* Mutation Studies. Unpublished report.
- Shell Research Ltd. (1990). Pivalic acid: A 28 Day Oral Toxicity Study in Rats. Unpublished report.
- Shell Research Ltd. (1993a). Acute Oral and Dermal Toxicity in Rat, Skin and Eye Irritancy in Rabbit and Skin Sensitizing Potential in guinea pigs. Unpublished report.
- Shell Research Ltd. (1993b). Versatic 913D: Bacterial Mutagenicity Studies. Unpublished report.
- Shell Research Ltd., (1993c). Versatic 913D: *In Vitro* Chromosome Studies Using Chinese Hamster Ovary (CHO) Cells. Unpublished report.
- TNO (1995a). Versatic 10: Bacterial Mutagenic Assay (Ames Test). Unpublished report.
- TNO (1995b). Chromosome Aberration Test in Cultured Human Lymphocytes with Versatic 10. Unpublished report.
- TNO (1995c). Assessment of Versatic 913D for Mutagenic Activity In Vivo in a Micronucleus

Test in Mice. Unpublished report.

- Vickers S, Duncan C, White S, Ramjit H, Smith J, Walker R, Flynn H and Arison B (1984). Carnitine and glucuronic acid conjugates of pivalic acid. *Xenobiotica* 15 (6): 453-458.
- Zepp R and Cline D (1977). Rates of direct photolysis in the aqueous environment. Environ. Sci. Technol. 11: 359-366.